REMARKS

Claims 1-8 are currently pending in the application. Claims 1-3 and 6-8 are in independent form.

The drawings are objected to in the Office Action because corrected drawings are required to be filed. Applicants have enclosed the corrected drawings as requested. Reconsideration of the objection is respectfully requested.

Claims 1 and 5-8 stand rejected under 35 U.S.C. §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action holds that the language "essentially of" is unclear and should be deleted from the claims. Applicants have amended the claims to read "selected from the group consisting of" to overcome this rejection. Reconsideration of this rejection is respectfully requested.

Claims 2-5 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,385,940 to Moskowitz. Specifically, the Office Action holds that the Moskowitz patent discloses L-arginine as a nitric oxide releasing compound. The Office Action further holds that claims 2-5 are directed to a compound and composition, and the intended use does not alter the compound and composition. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Moskowitz, as applied to the claims is respectfully requested. Anticipation has always

been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Moskowitz patent discloses administrating an NO donor compound to a stroke patient before or up to two hours after the stroke has occurred. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment. The Moskowitz patent also discloses that the brain/neurons cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz shows a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct."

Moskowitz merely states that the treatment of L-arginine reduces the size of an infarct in the brain after brain damage in a stroke. Moskowitz does not suggest that neurogenesis has occurred or would occur after administration of NO donors. The goal in Moskowitz is merely to prevent neuron death, not to regenerate neurons. There is no evidence that L-arginine can promote neurogenesis from the experiments in the Moskowitz patent.

In contradistinction, the presently pending claims are directed to a compound that promotes new neuron growth/neurogenesis. DETANONO administered to ischemic rats successfully produced neurogenesis, as evidenced by new neural cells and progenitor cells (Example 1). The ability to promote new neuron growth and neurogenesis is not an inherent property of L-arginine. As provided in Applicant's Declaration, the experiment of Moskowitz was performed and neurogenesis did not occur. If the ability to promote neurogenesis was an inherent property of L-arginine, one performing the experiment of Moskowitz should be able to find neurogenesis if looking for it after the administration of L-arginine. Following the protocol of the present invention however, demonstrates that neurogenesis does occur when an NO donor is administered to an ischemic rat.

Therefore, since the Moskowitz patent does not disclose a compound that promotes new neural growth or neurogenesis as set forth in the presently pending independent claims, the claims are patentable over the Moskowitz patent and reconsideration of the rejection is respectfully requested.

Claims 2, 3, and 4 stand rejected under 35 U.S.C. §102(b) as being anticipated by the Hindley, et al. reference (J. Neuroscience of Research 47:427-439). Specifically, the Office Action holds that Hindley, et al. teaches that cell cultures treated with NO donors such as sodium nitroprusside, contained a greater proportion of cell bearing neurites. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Hindley, et al., as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Hindley, et al. teaches an experiment wherein mouse hippocampal neurons and PC12 cells were plated onto tissue culture plates and coated with sodium nitroprusside (SNP) or sodium nitrate (SN), which released NO into solution. Cultures treated with SNP or SN were observed to have longer and more branched neurites than control cultures. (p. 430). Hindley, et al. does not have any evidence of neurite outgrowth *in vivo*, as all the experiments were performed *ex vivo*. Therefore, there is no indication that the NO donors in the Hindley, et al. reference can produce improvement of neurological function after a stroke or neural injury *in vivo*. Neurite outgrowth is produced from an existing neuron by a dendrite or axon elongating. The axons have growth cones on their leading edge to allow for navigation towards the cells with which the axon needs to associate. Neurite outgrowth is not neurogenesis. Hindley, et al. demonstrates no evidence of neurogenesis after applying NO donors to the cells.

In contradistinction, the present application discloses neurogenesis *in vivo* that results in improvement of neurological function after a stroke or neural injury. Specifically, the neurogenesis of the presently pending claims involves *new* neuron growth. This is critically different than neurite outgrowth. Neurogenesis is the development of new neuron cells, not growth from already existing neurons. The examples of the present application show that ischemic rats treated with DETANONO had newly formed neural cells (Example 1). "Increased numbers of new neurons were identified" when DETA/NO was administered after the onset of stroke (p. 15). Furthermore, treatment of ischemic rats with NO compounds increased the proliferation of progenitor cells (Example 1, p. 23). Progenitor cells are responsible for the creation of *new* neurons. The examples also show that administration of NO donor compounds improves neurological function in rats as a result of neurogenesis/new neuron formation (Example 2, p. 24-26).

Therefore, since the Hindley, et al. reference does not disclose neurogenesis *in vivo* resulting in improvement of neurological function as set forth in the presently pending independent claims, the claims are patentable over the Hindley, et al. reference and reconsideration of the rejection is respectfully requested.

Claim 2 stands rejected under 35 U.S.C. §102(b) as anticipated by either Nielsen, et al. (Am. J. of Crit. Care Med. Vol. 161:1154-1160 (2000)) or Poluha, et al. (Journal of Biological Chem. Vol. 272:38 24002-07). Specifically, the Office Action holds that Nielson, et al. teaches that NO donors are effective treatments of pulmonary

hypertension, and that Poluha, et al. teaches that NO acts as a regulator of cell proliferation which influences process outgrowth. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Nielson, et al. or Poluha, et al., as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Nielson, et al. teaches that NO donors can be used to reduce pulmonary hypertension in animals and that DETANONOate, a particular NO donor, decreases alveolar fluid clearance in rabbits. Nielson, et al. does not teach anything about neurogenesis or the use of NO donors in patients who have had a stroke or neural damage. There is no evidence of new neural cells forming because of the administration of DETANONOate in rabbits for pulmonary hypertension. There is no relationship between pulmonary hypertension or control of hypertension and neurogenesis. There is no relationship between hypertension and restoration of neurological function by neurogenesis. Controlling hypertension and neurogenesis are completely separate processes.

In contradistinction, the present application is directed to neurogenesis and improvement of function after a stroke or neural damage. The examples demonstrate that new neural cells and progenitor cells form in rats after administration of an NO donor compound. The present invention is not related in any way to controlling pulmonary hypertension.

Poluha, et al. teaches the use of a signal transduction pathway that blocks cell proliferation. Nerve growth factor (NGF) is applied to PC12 pheochromocytoma cells to induct nitric oxide synthase (NOS). NOS synthesizes nitric oxide (NO), which in turn activates p21 protein and $p53^{WAF1}$ protein to block cell proliferation. (Abstract, p. 24002, 3, 5) NO is acting as a regulator of cell proliferation, meaning that the presence of NO stops cells from proliferating. Poluha, et al. does not teach neurogenesis, and is not related to neurogenesis, which requires cell proliferation.

The present invention as claimed in claim 2 is distinguishable over Poluha, et al. since the NO donors administered induce neurogenesis and new neuron growth. The neurogenesis of the present invention has the opposite effect of the process in Poluha, et al., because neurogenesis is the proliferation of brain endogenous stem cells. The present invention discloses that new neural cells are produced due to the administration of NO donor compounds. Furthermore, blocking cell proliferation in the present invention would not lead to improved function after a stroke because new neurons would not be produced. There is no indication from Poluha, et al. that it would be desirable to administer NO to promote neuron growth.

Therefore, since the Nielson, et al. and Poluha, et al. references do not disclose the promotion of neurogenesis and new neural growth as set forth in the presently pending independent claims, the claims are patentable over the Nielson, et al. and Poluha, et al. references and reconsideration of the rejection is respectfully requested.

Claim 5 stands rejected under 35 U.S.C. §102(b) as anticipated by Schipp, et al. (Invert Neurosci 4:9-15 1999). Specifically, the Office Action holds that NO is involved in regulation of the vastonus when NO donors/precursors such as phosphodiesterase inhibitors are used. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Schipp, et al., as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Schipp, et al. teaches that NO can be a vasodilatatory mediator in regulating the diameter of blood vessels. Vasodilatation is not at all related to neurogenesis. Schipp, et al. does not teach anything about neurogenesis or new neural growth through the administration of an NO donor. In contradistinction, the present invention is directed to administering NO donor compounds to induce neurogenesis and the growth of new neurons.

Therefore, since the Schipp, et al. reference does not disclose neurogenesis and new neural growth as set forth in the presently pending claim, the claim is patentable over the Schipp, et al. reference and reconsideration of the rejection is respectfully requested.

Claims 1 and 6 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the Moskowitz patent ('940) taken with the Poluha, et al. reference, and Adams, et al (U.S. Patent No. 6,284,763). Specifically, the Office Action holds that Moskowitz teaches L-arginine is an NO donor but does not *per se* teach the promotion of neural

growth, and can also be administered to a stroke patient before, during, or after a stroke. Poluha, et al. teaches that NO is known to result in neural outgrowth of cells. The Office Action further holds that Adams, et al. teaches systemic routes for administering NO and that NO donors can be administered to patients to reverse pathologic vascular degradation. Therefore, one skilled in the art would have known to add NO to promote neural outgrowth for treatment of stroke where neurological impairment occurs. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Moskowitz patent, the Poluha, et al. reference, and the Adams, et al. patent is respectfully requested.

It is Hornbook Law that before two or more references may be combined to negate patentability of a claimed invention, at least one of the references must teach or suggest the benefits to be obtained by the combination. This statement of law was first set forth in the landmark case of Ex parte McCullom, 204 O.G. 1346; 1914 C.D. 70. This decision was rendered by Assistant Commissioner Newton upon appeal from the Examiner-in-Chief and dealt with the matter of combination of references. Since then, many courts have over the years affirmed this doctrine.

The applicable law was more recently restated by the Court of Appeals for the Federal Circuit in the case of ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572,1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984). In this case the Court stated, on page 933, as follows:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103 teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any such suggestion or incentive. Accordingly we hold that the court below erred as a matter of law in concluding that the claimed invention would have been obvious to one of ordinary skill in the art under section 103."

This Doctrine was even more recently reaffirmed by the CAFC in Ashland Oil, Inc. v. Delta Resins and Refractories, Inc., et al., 776 F.2d 281,297, 227 U.S.P.Q. 657,667. As stated, the District Court concluded:

> "Obviousness, however, cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art, which would have made such a combination appropriate."

The Court cited ACS Hospital Systems, Inc. in support of its ruling. This Doctrine was reaffirmed in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995).

As discussed above, the Moskowitz patent discloses administrating an NO donor compound to a stroke patient before or up to two hours after the stroke has occurred, but does not disclose neurogenesis or new neural growth resulting from the administration of an NO donor compound.

One would not look to Poluha, et al. to improve the stroke treatment disclosed in Moskowitz. As discussed above, Poluha, et al. is not related to neurogenesis. In fact, looking at Poluha, et al. would confirm the evidence in Moskowitz that the nervous system cannot regenerate, since Poluha, et al. shows that administrating NO donors blocks cell proliferation. Neither of these references alone or combined

demonstrate that neurogenesis occurs when an NO donor compound is administered.

Adams, et al. discloses administering an anti-pressor agent such as an NO donor to remodel vasculature and is concerned with improving blood flow to arteries by increasing radial size. Adams, et al. is not at all related to neurogenesis or new neuron growth. Improving blood flow is irrelevant to neurogenesis and recovering function after a stroke. Applying the method of Adams, et al. to the invention of Moskowitz would only increase the blood flow in the stroke victim and would do nothing to promote neurogenesis.

The present application provides examples of the opposite result of Poluha, et al. – that NO donors enhance cell proliferation. The present invention also is not related to improving blood flow to arteries. The combination of either Poluha, et al. or Adams, et al. with Moskowitz would not lead to the present invention. The examples of the present invention show that the administration of NO donor compounds promotes neurogenesis and new neuron growth, and therefore the present invention is patentable over the combination of Moskowitz, Poluha, et al. and Adams, et al.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the

combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 7 and 8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the Moskowitz patent ('940), taken with the Poluha, et al. reference, and the Adams, et al. patent ('763), and further in view of Van Wagenen, et al (J. Neurobiology Vol. 39:2 168-185 (1999)). Specifically, the Office Action holds that Van Wagenen, et al. teaches that growth cones serve sensory and motor functions and L-arginine is a sensitizing agent. Therefore, it would have been obvious to combine the Moskowitz, Poluha, et al. and Adams, et al. teachings that administering NO effects neural growth with those of Van Wagenen, et al. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Moskowitz patent, the Poluha, et al. reference, the Adams, et al. patent, and the Van Wagenen, et al. reference is respectfully requested.

Van Wagenen, et al. teaches that NO donors caused an elongation of filopodia and reduction of number of filopodia on the growth cones of snail neurons. Filopodia extend from the leading edge of a growth cone, aiding in the growth cone's navigational abilities, therefore serving sensory and motor functions *for the growth cone*. The filopodia are not involved in the overall motor and sensory functions of the brain and body. Van Wagenen, et al. teaches that low concentrations of NO acts as a cue that increases a neuron's growth cone action radius by the elongation of filopodia. (p. 183) Thus, NO donors can affect the ability of a growth cone to move

toward a particular synapse to make a neuronal connection. Van Wagenen, et al. does not teach anything about neurogenesis or the recovery of function in the brain after a stroke or neural injury. There is no evidence that the mobility of existing growth cones can increase brain functionality or cognitive ability after a stroke or neural injury.

The presently pending claims are directed to increasing neural/cognitive function from neurogenesis and new neural growth. As described above, neurogenesis and new neural growth is unrelated to neurite outgrowth, wherein already existing neural growth cones navigate to associate with a particular synapse. Applying the teachings of Van Wagenen, et al. to the combination of Moskowitz, Poluha, et al. and Adams, et al. as discussed above, would only suggest that NO donors can increase growth cone mobility in a stroke victim, not that new neurons can be formed or that function can be recovered in the brain after a stroke or neural injury. Therefore, the combination of Moskowitz, Poluha, et al. and Adams, et al. in view of Van Wagenen, et al. does not suggest a method of increasing neural or cognitive function from new neural growth by the administration of NO donors.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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